FACSIMILE COVER SHEET

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TO:	Examiner Ilia I. Ouspenski	**FROM:**	Frank C. Eisenschenk, Ph.D.
COMPANY:	U.S. Patent Office	**DATE:**	July 30, 2010
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SUBJECT/MESSAGE:

Re: U.S. Patent Application Docket No. ISI.103
RECEPTOR MODULATORS
(Davis)
Serial No. 10/585,491; filed July 7, 2006

Dear Examiner Ouspenski: In accordance with your request, attached is page 9 of the Amendment dated July 16, 2010.

antibodies to PD-1 is restricted to the sequence LAAFPEDRSQPGQDCR (SEQ ID NO: 61) and the Office Action provides no evidence that the antibodies made to this sequence would be expected to bind to epitopes containing amino acids other than this specific sequence (*e.g.*, discontinuous epitopes containing the sequence). Applicant also notes that antibodies that bind to only this sequence are also outside the scope of the claims.

Applicant further notes that the substitution of a single amino acid in the sequence of a protein is sufficient to render the protein resistant to binding (neutralization) by both polyclonal and monoclonal antibodies. For example, Watkins *et al.* (attached with this response) clearly demonstrate that single and double mutations in the sequence of HIV-1 envelope protein abrogate antibody binding to, and neutralization of, HIV-1 and that a single amino acid mutation is sufficient to alter the conformation of the polypeptide such that antibodies do not bind to the protein at multiple epitopes (see Abstract and page 8436, last paragraph). Indeed, Watkins *et al.* indicate that numerous studies have illustrated how changes in one region of a protein produce alterations in noncontiguous regions of that protein. In this case, it is unclear how antibodies that were generated against the LAAFPEDRSQPGQDCR (SEQ ID NO: 61) peptide would be expected to bind to an epitope comprising PALLVV (SEQ ID NO: 44) or an epitope comprising SEQ ID NO: 61 (*e.g.*, a discontinuous epitope containing SEQ ID NO: 61) since Hunig *et al.* fail to teach the production of antibodies to such an epitope and those skilled in the art would have known that changes in the amino acid sequence of the epitope to which the antibody was raised would have reasonably been expected to abrogate antibody binding. Accordingly, reconsideration and withdrawal of the rejection set forth over Hunig *et al.* is respectfully requested.

Turning, next, to the rejection over Wood *et al.*, Applicant respectfully submits that this reference also fails to teach or anticipate the claimed antibody. While Applicant acknowledges that "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer" (*Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999)), Applicant also notes that, in order to anticipate, a prior art reference must also provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo*